REMARKS

Applicant wishes to thank Examiner Huynh and Supervisory Examiner Chan for their time spent preparing for and conducting the telephonic interview with the undersigned on October 6, 2003 ("the interview"). The remarks below substantially incorporate the substance of the interview.

Claims 20, 42, 44, 47 and 59 have been amended. No claims have been added. No claims have been deleted. With entry of this amendment, claims 2-6, 11, 17, 18, 20-22, 42, 44, 47 and 49-64 will be pending.

Applicant respectfully traverses each of the rejections in the Office action for the reasons set forth below.

Objections to the Claims

Claim 20 has been amended to address the objection related to a missing comma.

Claim 42 has been amended to address the spacing objection.

Claim 47 has been amended to address the objection. Claim 47 now depends from claim 44.

Rejections under 35 U.S.C. § 112

Claims 2-6, 11, 17-18, 20-22, 44, 47 and 49-64 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Claims 2-6, 11, 17-18, 20-22, 44, 47 and 49-64 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The 112 rejections were discussed during the interview. It was agreed that the claims would be amended to specify that Z is one of the side chains represented by formula (IIIA) or formula (IIIB) on pages 11 and 12 of the specification. It was further agreed that specifying that the target molecule moiety is linked to the vitamin D moiety at the C-1, C-3, C-24 or C-25 position would overcome the 112 rejections. Applicant has

amended independent claims 20, 44 and 59 as previously discussed, but still contends that the claims satisfied the enablement and written description requirements in their pre-amended form.

Claim 42 was rejected under 35 § U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 42 has been amended to address this rejection.

In view of the amendments, withdrawal of the 112 rejections is respectfully requested.

Rejection under 35 U.S.C. § 102(b): Bouillon

Claims 20, 44, 49-51, 53-56, 58-62 and 64 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,232,836 issued to Bouillon ("Bouillon"). Independent claims 20, 44 and 59 are recited above.

The Examiner contends that Bouillon teaches "that conjugates can be linked to the vitamin D moiety at the C-1, C-3, C-24 or C-25 position (see column 4, lines 19-45)." Office action, page 8. But the portion of Bouillon to which the Examiner cites actually discloses prior art conjugates. Moreover, Bouillon states this about these prior art conjugates:

> However, these haptens are not entirely satisfactory, inasmuch as the 22-position of branching is still in proximity to the 24- and 22-positions where hydroxyl groups specific for recognition of several metabolites of vitamin D_3 are bound.
>
> These problems of steric hindrance arise in the same way for the production of radioactive (I-125) or enzyme-labeled tracers, which require chemical branches identical to those described above. Consequently, the branches already described do not enable such tracers to be obtained.

Col. 28, lines 33-41.

In other words, Bouillon actually teaches away from these other conjugates, indicating that its "present invention proposes previously presented vitamin D derivatives possessing a branch at the 11-position, these derivatives being useful as drugs and also for preparing radioisotopic or enzyme-labeled tracers for assays of metabolites of vitamin D including those *having a hydroxyl group at the 1-, 24-, 25- or 26-position*, and as haptens for the purpose of preparing immunogens and hence antibodies in the case of immunoassays." Col. 4, lines 56-64, emphasis added. Not only do Bouillon's vitamin D derivatives focus only on linking at the C-11 position, the

derivatives are being used for an entirely different purpose, namely, for preparing tracers, immunogens and antibodies. Regardless, none of the prior art conjugates show conjugates having Applicant's claimed targeting molecules at Applicant's claimed positions.

The Examiner seems, in part, to recognize this by stating: "[h]owever, the advantage of linking the compound at the carbon 11 position of the vitamin D moiety offers the possibility of introducing chosen modifications of vitamin D without interfering directly with the functions of vitamin D." *Id.* Bouillon, however, is limited to conjugates linked at the C-11 position, whereas Applicant claims linking at the C-1, C-3, C-24 or C-25 positions. In fact, the Examiner alludes to "the possibility of introducing at the 11α- or 11β-position substitutions which increase or antagonize the activity of 1α 25-$(OH)_2$-vitamin D, either overall, or in respect of specific targets (immune, cancer, skin, endocrine, cardiovascular and bone cells, and the like) opens up previously presented prospects for applications." Col. 29, lines 18-23. No mention is made of specific targeting when the C-1, C-3, C-24 or C-25 positions are employed. In fact, Bouillon only mentions specific targeting with respect to the C-11 position, as set forth in the previous excerpt. Furthermore, Bouillon provides no reasonable expectation that the benefits of C-11 linking would adhere to linking at the other positions. Instead, Bouillon suggests these benefits are unique to the C-11 position. Applicant respectfully invites the Examiner to cite a specific portion of Bouillon in which targeting using the C-1, C-3, C-24 or C-25 positions is taught or suggested.

Accordingly, independent claim 20 and its dependent claims 21-22 and 54-58, independent claim 44 and its dependent claims 2-6, 11, 17-18, 47-53 and 65, as well as independent claim 59 and its dependent claims 60-64 are all allowable over Bouillon. Reconsideration of these claims and withdrawal of the 102 rejection are respectfully requested.

Claim Rejections under 35 U.S.C. § 103(a): Bouillon in view of Bauss or Orme or P&G

Claims 11, 17-18, 20, 44, 47, 49, 52, 54, 57, 59-60, and 63 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bouillon in view of Bauss et al. (Calcif Tissue Int 59: 168-173, 1996; PTO 892) or Orme et al. (of record, Bioorg Med Chem Lett 4: 1375-1380, 1994; PTO 892) or WO 92/21355 (December 1992, PTO 892) assigned to P & G ("P&G").

More particularly, the Examiner contends that Bouillon differs from Applicant's claims, only in that it does not show a targeting molecule bisphosphonate or calcitonin. Moreover, the

Examiner contends that the claimed invention in claim 11 differs from the teachings of the reference only that the conjugate wherein the bifunctional connector is an amino acid chelated to the target molecule moiety and linked to the vitamin D moiety via an amide linkage. The Examiner also states that the claimed invention in claim 17 differs from the teachings of the reference only that the conjugate further comprises at least one therapeutic agent other than vitamin D moiety conjugated therewith. Office action, page 11.

Overall, it appears that the gravaman of the Examiner's obviousness rejection is predicated on Bouillon teaching each of the limitations of independent claims 20, 44 and 59. In other words, it appears that the Examiner is relying on the Bauss, Orme and P&G to show some of the features of the dependent claims, rather than the independent claims. Therefore, Applicant respectfully submits that the Examiner's argument fails because Bouillon does not teach each of the limitations of the base independent claims for the reasons discussed above. Therefore, independent claims 20, 44 and 59 are allowable.

Although the Examiner has cited the secondary references to show some of the limitations of the dependent claims, Applicant will still comment on the full propriety of the Examiner's 103 rejection.

To establish prima facie obviousness: 1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings; 2) there must be a reasonable expectation of success; and 3) the references must teach or suggest all of the claimed limitations. MPEP 2142. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicant respectfully submits that a prima facie case of obviousness has not been established. First, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the references. Moreover, one of ordinary skill in the art would not reasonably expect such a combination to succeed for the reasons set forth below.

Even assuming *arguendo* that the references are combinable, the combination still would not teach or suggest the claimed limitations. More particularly, the Examiner's 103 argument fails because, again, it assumes that Bouillon teaches each of the limitations of the independent

claims. As discussed above, however, with respect to the 102 rejection, Bouillon does not teach, suggest or enable linking of the claimed target molecule moiety at the claimed C-1, C-3, C-24 or C-25 positions. Bouillon teaches away from these positions, touting the advantages of linking at the C-11 position. Consequently, even if one of skill were somehow motivated to combine Bouillon with Bauss, Orme or P&G, Bouillon's deficiency still would not be cured.

Accordingly, independent claim 20 and its dependent claims 21-22 and 54-58, independent claim 44 and its dependent claims 2-6, 11, 17-18, 47-53 and 65, as well as independent claim 59 and its dependent claims 60-64 are all allowable with respect to Bouillon combined with Bauss, Orme or P&G. Reconsideration of these claims and withdrawal of the 103 rejection are respectfully requested.

Rejection under 35 U.S.C. § 102(b): Capelli

Claims 2-6, 11, 17-18, 20, 44, 49-51, 53-56, 58-62 and 64 stand rejected under 35 U.S.C. § 102(b) as being anticipated by WO 92/14493 assigned to Capelli ("Capelli").

The Examiner contends that Capelli teaches "a pharmaceutical composition comprising a conjugate wherein the reference conjugate compris[es] vitamin D compounds or its analogs which inherently ha[ve] the formula recited in instant claims 20, 44 and 59 linked to a targeting moiety such as an estrogen that targets the bone (See claims 1-5, in particular)." Office action, page 9, paragraph 13. Applicant respectfully traverses this assertion. More particularly, claims 1-5 of Capelli only disclose "a targeting agent for the intracellular delivery of a therapeutic or diagnostic agent, comprising a conjugate comprised of (i) a non-protein molecule which binds an intracellular hormone receptor, (ii) a therapeutic or diagnostic agent and (iii) a linker moiety joining said agent to said non-protein molecule." Claim 3 specifies that the non-protein molecule may be an estrogen or a vitamin D compound. Nowhere in these claims, however, is a vitamin D moiety being associated with estrogen, or any of the claimed targeting molecules, taught or suggested. More particularly, Capelli is concerned with using non-protein molecules to deliver therapeutic or diagnostic agents, via a linker molecule. Capelli classifies vitamin D compounds and estrogen as separate examples or species of non-protein molecules, which can be used as a delivery mechanism (see claim 3 of Capelli in which both estrogen and vitamin D compounds are listed as non-protein molecules). Capelli is not directed to delivery of vitamin D itself. Instead, it focuses on using vitamin D as a targeting molecule, just as it focuses on using

estrogen as a targeting molecule. But, again, Capelli does not teach or suggest using estrogen and vitamin D compounds together.

Nevertheless, the Examiner further contends that Capelli teaches various "conjugates such as vitamin D linked [to] a targeting moiety such as anti-estrogen, thyroid hormone, boron or tetracyclines via a connecting group such as poly-L-Lysine or a bifunctional connector such as ethylene diamine to form a bond therebetween (See page 6, lines 4-30, claim 5, page 8, line 4, in particular). The reference conjugate is useful for intracellular delivery of therapeutic or diagnostic agent[s] (See claim 5)." Office action, page 9, paragraph 13. Each of independent claims 20, 44 and 59, to the contrary, specifies target molecule moieties comprising calcitonin, a bisphosphonate, a phosphate, polyaspartic acid, polyglutamic acid, an aminophosphosugar, osteonectin, bone sialoprotein, osteopontin, estrogen, dehydroepiandrosterone (DHEA), a metal ion-amino acid chelate, and combinations thereof. Capelli makes no mention of any of these claimed target molecule moieties, except for estrogen. And Capelli only describes estrogen as being a suitable intracellular receptor binding molecule, along with vitamin D compounds. Page 5, lines 33-37. Again, Capelli does not mention, let alone enable, the vitamin D compounds being associated with estrogen. To the contrary, Capelli discloses linking a therapeutic or diagnostic agent to either vitamin D or estrogen (among others) via a linking molecule.

Finally, Applicant respectfully submits that the Examiner may have misread Capelli, by contending that targeting moieties "such as anti-estrogen, thyroid hormone, boron or tetracyclines" are disclosed. *Id.* A closer read of Capelli, however, indicates that anti-estrogens and thyroids are alternative intracellular receptor binding molecules to vitamin D compounds and estrogen. Boron and tetracyclines are actually the therapeutic or diagnostic agents being delivered.

Accordingly, independent claim 20 and its dependent claims 21-22 and 54-58, independent claim 44 and its dependent claims 2-6, 11, 17-18, 47-53 and 65, as well as independent claim 59 and its dependent claims 60-64 are all allowable with respect to Capelli. Reconsideration of these claims and withdrawal of the 102 rejection are respectfully requested.

Claim Rejections under 35 U.S.C. § 103(a): Capelli in view of Bouillon and Bauss or Orme or P&G

Claims 20, 44, 47, 49, 52, 54, 57, 59-60, and 63 stand rejected under 35 U.S.C. 103 (a) as being unpatentable over Capelli in view of Bouillon and Bauss or Orme.

The Examiner contends that the claimed invention in claims 20, 44, 49, 52, 54, 57, 59-60, and 63 differs from the teachings of the reference only that the conjugate wherein the targeting molecule is bisphosphate or calcitonin. Furthermore, she contends that the claimed invention in claim 47 differs from the teachings of the reference only that the conjugate wherein the bisphosphonate is linked to said vitamin D moiety at a position on the vitamin D moiety which is C-1, C-3, C-24 or C-25.

Overall, it appears that the gravaman of the Examiner's obviousness rejection is predicated on Capelli teaching each of the limitations of independent claims 20, 44 and 59. In other words, it appears that the Examiner is relying on Bouillon, Bauss, Orme and P&G to show some of the features of the dependent claims, rather than the independent claims. Therefore, Applicant respectfully submits that the Examiner's argument fails because Capelli does not teach each of the limitations of the base independent claims. Therefore, independent claims 20, 44 and 59 are allowable.

Although it appears that the Examiner has cited the secondary references to show some of the limitations of the dependent claims, Applicant will still comment on the full propriety of the Examiner's 103 rejection.

To establish prima facie obviousness: 1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings; 2) there must be a reasonable expectation of success; and 3) the references must teach or suggest all of the claimed limitations. MPEP 2142. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicant respectfully submits that a prima facie case of obviousness has not been established. First, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the

references. Moreover, one of ordinary skill in the art would not reasonably expect such a combination to succeed.

Even assuming *arguendo* that the references are combinable, the combination still would not teach or suggest the claimed limitations. More particularly, the Examiner's 103 argument fails because, again, it assumes that Capelli teaches each of the limitations of the independent claims. Nevertheless, the Examiner contends that "it would have been obvious to ... substitute the estrogen in the vitamin D conjugate as taught by [Capelli] for the bisphosphate as taught by [Bouillon] or the calcitonin as taught by P&G for a conjugate comprising a vitamin D moiety associated with bisphosphate or calcitonin associated at the C-1, C-3, C-24, C-25 or C11 positions as taught by [Bouillon]." Office action, page 17. As discussed above, however, with respect to the 102 rejection, Capelli does not mention, let alone enable, the vitamin D compounds being associated with estrogen, or any other targeting molecule for that matter. Again, Bouillon does not teach, suggest or enable linking at the C-1, C-3, C-24 or C-25 positions as claimed. Bouillon teaches away from these positions, instead solely touting the advantages of linking at the C-11 position. Consequently, even if one of skill were somehow motivated to combine Capelli with Bouillon, Bauss, Orme or P&G, Capelli's deficiencies would still not be cured.

Accordingly, independent claim 20 and its dependent claims 21-22 and 54-58, independent claim 44 and its dependent claims 2-6, 11, 17-18, 47-53 and 65, as well as independent claim 59 and its dependent claims 60-64 are all allowable with respect to Capelli in view of Bouillon and Bauss or Orme or P&G. Reconsideration of these claims and withdrawal of the 103 rejection are respectfully requested.

Claim Rejections under 35 U.S.C. § 103(a): Bouillon in view of Bauss or Orme and further in view of Hatano

Claims 21-22 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Bouillon in view of Bauss or Orme as applied to claims 11, 17-18, 20, 44, 47, 49, 59, 54, 57, 59-60, and 63 mentioned above and further in view of U.S. Patent No. 6,309,666 issued to Hatano ("Hatano"). Claims 21 and 22 depend from allowable independent claim 20, and are therefore allowable for the same and similar reasons. Claims 21 and 22 may have additional patentable subject matter. Reconsideration and allowance of claims 21 and 22 are respectfully requested.

Claim Rejections under 35 U.S.C. § 103(a): Capelli in view of Bouillon and Bauss or Orme and further in view of Hatano

Claims 21-22 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Capelli in view of Bouillon and Bauss or Orme as applied to claims 20, 44, 47, 49, 52, 54, 57, 59-60, and 63 mentioned above and further in view of Hatano. Claims 21 and 22 depend from allowable independent claim 20, and are therefore allowable for the same and similar reasons. Claims 21 and 22 may have additional patentable subject matter. Reconsideration and allowance of claims 21 and 22 are respectfully requested.

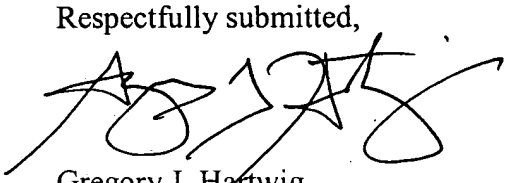
Claim Free of Prior Art

Finally, the Examiner indicated that claim 42 is free of prior art. Claim 42 previously depended on claim 44. Claim 42 has been rewritten in independent form. Redundancies have been deleted from amended claim 42. During the interview, the Examiner indicated that claim 42 would be allowable once the 112 rejection was addressed. Accordingly, allowance of claim 42 is respectfully requested.

CONCLUSION

Applicants respectfully request allowance of the application. Should any issues remain, the Examiner is strongly encouraged to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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